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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,850	09/04/2003	James A. Carnazza	18184-00001	5271

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,850	CARNAZZA, JAMES A.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/4/03*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *2-5 and 9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claims 1 (in part) and 2 - 5, drawn to methods of inhibiting the development of Huntington's disease by determining a trinucleotide repeat pattern, establishing a serum level, and administering a hormone, classified in class 514, subclass 169, for example.

   II. Claims 1 (in part) and 6 - 8, drawn to methods of inhibiting the development of Huntington's disease, comprising predetermining the rate at which one or more hormones binds to polyglutamines, classified in class 514, subclass 169, for example.

   III. Claims 9 - 12, drawn to methods of determining the optimum time for administering a hormone, classified in class 436, subclass 71, for example.

2. The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to methods which require different steps. The additional steps are required for group II (i.e. claims 6 – 8), but are not for group I. Because the additional steps are required, group II is deemed to be patentably distinct from group I. Furthermore searches for the two groups are not expected to be coextensive, as consideration of group II requires searching for different methods steps than consideration of group I. Therefore there would be a serious burden on the examiner if goups I and II were to be considered together.

Inventions I and II are not related to Invention III. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are drawn to different methods with different goals and different steps. Groups I and II are drawn to methods of treating disease, whereas group III is drawn to a method of determining a time. Groups I and II require administration of compounds to patients, which is not required for group III. Furthermore because the searches for groups I

and II are not coextensive with group III, there would be a serious burden on the examiner if either group I or II were to be considered together with group III.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

4. During a telephone conversation with Jennifer Haeckl on 19 July 2005 a provisional election was made without traverse to prosecute the invention of Group II, claims 1 (in part and 6 – 8). Affirmation of this election must be made by applicant in replying to this Office action. Claims 2 – 5 and 9 – 12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1 and 6 – 8 are under examination.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

6. The oath or declaration is defective because: the filing date listed for provisional application is incorrect. The actual filing date is 4 September 2002, but the oath lists 4 September 2003 as the filing date. Correction is required.

Priority Determination

7. 35 U.S.C. § 120 states that:

> An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

35 U.S.C. § 119(e) states that:

> An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional

application was filed and if it contains or is amended to contain a specific reference to the provisional application.

8. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 120 or § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first paragraph, with respect to the now claimed invention. Provisional application 60/408184, filed 4 September 2002, does not provide a description of how to practice the claimed methods, does not disclose any data, and therefore does not constitute an enabling disclosure. Similarly provisional application 60/443,397 does not disclose any data or provide a description of how to practice the claimed methods and therefore does not constitute an enabling disclosure. Therefore priority is set at the instant filing date, 4 September 2003. Should applicant argue that the provisional applications in fact are enabling disclosures, applicant should provide evidence of such, for example by pointing out the page and line numbers where the results of the experiments appear.

Claim Objections

9. Claim 1 is objected to because of the following informalities: it is grammatically incorrect. The claim recites "determining that the individual exhibits... is of a sufficient ...". The examiner suggests deleting the words "is of a" and "number". Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1 and 6 – 8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the amount of estradiol bound to huntingtin protein *in vitro*, does not reasonably provide enablement for inhibiting the development of Huntington's disease, or for determining the rate of binding of estradiol to huntingtin, or for determining trinucleotide repeat patterns in any nucleic acid, or for administering sufficient amounts of a compound to an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Bonelli et al. (2004. Expert Opin. Pharmacother. 5:767-776) teach that the treatment of Huntington's disease is difficult and complex (see particularly p. 768, first paragraph of section 2 and p. 772, section 5), indicating that the level of predictability in the art is low. The specification discloses that estradiol binds with stronger affinity to huntingtin protein with 63 glutamines than to the protein with 47 glutamines, and with stronger affinity to the 47-glutamine protein than to the 23-glutamine protein (see p. 12).

The claims are drawn to methods for inhibiting the development of Huntington's disease comprising administering estrogen or testosterone to an individual, but there is no disclosure of administration of either of these to an individual. There is no disclosure of amelioration of any symptoms, in an animal model or in a person, related to Huntington's disease. The only data presented are on the binding of estradiol to Huntington proteins with varying numbers of glutamines. A skilled artisan would not be able to conclude, based on the state of the art, and the data presented, that administering either estrogen or testosterone to a patient at risk of developing the disease, will in fact ameliorate any symptoms or inhibit the development of Huntington's disease as claimed. In fact, the art recognizes that administration of estrogens mimics some of the symptoms of Huntington's disease. For example, Bausieda et al. (1979. Neurology 29:1605-1609) teach that administration of oral contraceptives, which are estrogens, can induce chorea, and chorea is a symptom of Huntington's disease (see Bonelli p. 767). Additionally, Ott et al. (2002. Journals of Gerontology: Medical Sciences 57A:M594-M598) teach that estrogen therapy does not attenuate cognitive declines in the elderly, and dementia is also a symptom of Huntington's disease (see Bonelli p. 768). Furthermore Bonuccelli (1992. Advances in Biochemical Psychopharmacology 47:149-154) teaches that administration of estradiol at 100 ug per day for three months does not improve either the motor or cognitive symptoms of Huntington's disease in human patients.

Furthermore, claim 1 is drawn to the administration of either estrogen or testosterone, but these are known to have opposite effects when administered to animals. For example,

Eckert (1988. Animal Physiology. pp. 314 - 318) teaches estrogen promotes the development and maintenance of female characteristics, whereas testosterone promotes the development of male characteristics. A skilled artisan would not expect the two compounds to be interchangeable, given their vastly different effects on mammals, and the lack of working examples of administration of either estrogen or testosterone or a precursor thereof to an individual. Claim 1 is also drawn to administration of sufficient amounts of the compounds to individuals. However there is no guidance provided in the specification as to what constitutes a sufficient amount, nor is there guidance as to how to determine what amounts are sufficient for the inhibition of Huntington's disease. Thus an artisan would have to resort to undue experimentation in order to determine what constitutes a sufficient amount, given the lack of guidance and the unpredictability in the art.

Claims 1 recites "determining that the individual exhibits a trinucleotide repeat pattern... sufficient number to indicate a risk for developing Huntington's disease". There is no requirement that the huntingtin gene be examined for the number of trinucleotide repeats present. Bonelli teaches that expanded trinucleotide repeats in huntingtin are associated with an increased risk of developing the disease (see p. 767). However, a skilled artisan would be aware that many other diseases, including spinal and bulbar muscular atrophy, spinal-cerebellar ataxia, and several others are all characterized by an increase in the number of these trinucleotide repeats in different proteins (see Piccioni et al. 2001. Brain Research Bulletin 56:215-220, particularly the paragraph spanning pp. 215 – 216). But since no protein other than huntingtin has been conclusively shown to be so correlated with Huntington's disease, the artisan would recognize that detecting trinucleotide repeats in genes other than huntingtin would not indicate a susceptibility to Huntington's disease.

Claim 1 includes establishing that a serum level of a preselected hormone is below normal. The specification does not provide guidance as to how to select the hormone. The only examples in the specification are drawn to estrogen. There are no examples drawn to any other hormone, and the specification does not guide the artisan in selection of a hormone. Therefore the artisan would have to resort to undue experimentation to know which hormone to select for establishing a serum level. The artisan would have to systematically test all hormones, as the claim does not limit the hormones to be measured to estrogen or testosterone; that limitation appears only in the administration step. Then the artisan would have to determine which hormones are decreased in patients with trinucleotide repeat patterns sufficient to indicate a risk of developing Huntington's disease. Because of the breadth of the claims and the lack of

guidance provided by the specification, the amount of experimentation required to preselect the hormone would be undue. Claim 1 also recites establishing a serum level of a hormone of an individual "is below normal", but there is neither disclosure nor guidance as to what constitutes normal. Estradiol levels vary at least 3-fold across the course of the reproductive cycle (see Eckert pp. 319 – 320), so detecting a low level is meaningless in the absence of knowing the phase of the subject's reproductive cycle. Similarly both estrogen and testosterone increase and decrease across the life cycle, being low at birth, higher at puberty, and decreasing in advanced age. The specification does not provide guidance as to what constitutes a normal level of estrogen or testosterone, thus a skilled artisan would have to resort to undue experimentation in order to determine normal levels and then compare the subject's levels to the normal levels.

Claim 6 recites the limitation "predetermining the rate at which one or more of said hormones binds...". The specification discloses the results of experiments in which the amount of binding was determined at a single time. There is no disclosure of the rate of binding of estradiol to huntingitn. Rates are expressed as amount per unit time, but since there is only one time point disclosed a skilled artisan could not possibly determine the rate. Furthermore the differences in binding observed could be explained by differences in either the rates of binding or in the total amount of binding. A skilled artisan would have to resort to undue experimentation in order to determine the rates of binding between estradiol and huntingtin protein.

Claim 6 also recites that the artisan should determine an optimum amount of time to begin administering the hormones, but does not indicate how that amount of time should be determined. There are no examples in the specification of determining what the time interval is, and there is not guidance on how to determine the interval.

Claim 8 is drawn to a particular amount of radioactivity, expressed in counts per minute. The number of counts per minute of radioactivity in a sample is dependent on the amount of starting material (i.e. labeled estradiol in this case), the specific activity of the material, the amount of time that has passed since the specific activity was measured, the isotope used, the sensitivity of the gamma counter, and the distance from the radioactive source to the counter. There is no disclosure of the specific activity of the starting material, the amount of time that had passed since the specific activity was calculated, the sensitivity of the counter, or the distance between the counter and the sample. A skilled artisan would thus have to resort to undue experimentation in order to replicate applicant's results expressed in counts per minute, as the

artisan would have to manipulate multiple variables. Furthermore, because 50,000 cpm can be obtained simply by increasing the amount of starting material, an artisan would not conclude that said measurement is indicative of binding. Finally, the claim does not indicate whether the supernatant or pellet should be measured; in applicant's assay described on p. 12 of the specification the supernatant was counted, but the artisan would recognize that a large amount of radioactivity would remain in the pellet and column.

For all these reasons, a skilled artisan would have to resort to undue experimentation in order to make and use the invention commensurate in scope with the claims.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1 and 6 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: administering the hormone to the individual identified as having a specific trinucleotide repeat pattern and having a decreased level of a preselected hormone. A skilled artisan would not be able to determine the metes and bounds of this claim, because the administration step is confusing in the absence of identification of a population to whom the drug is to be administered.

14. Claims 6 – 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "said huntingtin polyglutamine protein" in lines 2 - 3. There is insufficient antecedent basis for this limitation in the claim. The claim depends from claim 1, which is drawn to trinucleotide repeat patterns in unspecificed nucleic acids.

Claim 8 recites the limitation "said affinity" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 8 depends from claim 6, which is not drawn to affinity.

Claim 8 is considered indefinite because it recites the limitation "equal to or less than about 50,000 counts per minute". The number of counts per minute of radioactivity in a sample is dependent on the amount of starting material (i.e. labeled estradiol in this case), the specific activity of the material, the amount of time that has passed since the specific activity was measured, the isotope used, the sensitivity of the gamma counter, and the distance from the

radioactive source to the counter. There is no disclosure of the specific activity of the starting material, the amount of time that had passed since the specific activity was calculated, the sensitivity of the counter, or the distance between the counter and the sample. The claim is indefinite because the number of cpm can vary widely and does not necessarily correlate to the amount of estradiol present in the sample. Thus a skilled artisan would not be able to determine the metes and bounds of claim 8.

Conclusion

15. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

1) Koller et al. 1982. Neurology 32:547-549

2) Heron et al. 2000. Metabolic Brain Disease 15:267-274

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker
August 11, 2005

SHARON TURNER, PH.D.
PRIMARY EXAMINER
8-15-05